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Advantage of Surgery and Adjuvant Chemotherapy in the Treatment of Primary Gastrointestinal Lymphoma

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Background: Surgery has been the mainstay of treatment for gastrointestinal (GI) lymphoma. The role of adjuvant chemotherapy to surgery has not been clearly elucidated.

Methods: The review covered 100 patients who were diagnosed with primary GI lymphoma and treated from 1980 to 1993 at Providence Hospital (Southfield, MI), and Hartford and St. Francis Hospitals (Hartford, CT) with a median follow-up of 5 years. Forty-two patients were treated with surgery alone; 31 patients with surgery and adjuvant chemotherapy; 23 patients with primary chemotherapy, and 4 patients received no treatment.

Results: The 5-year actuarial survival based on the above treatments calculated by life-table analysis were 57%, 76%, 58%, and 0%, respectively. This series showed that surgery with adjuvant chemotherapy significantly improved the 5-year actuarial survival of patients with primary GI Lymphoma and that primary chemotherapy showed comparable survival to surgery alone. There was no difference in prognosis when comparing patients with different stage, grade, or location of disease in the GI tract.

Conclusions: We recommend surgery when feasible with adjuvant chemotherapy as the mainstay of treatment for primary GI lymphoma. However, if a patient presents with comorbid factors, primary chemotherapy offers an effective alternative.

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KEY WORDS: gastric; intestinal lymphoma; primary chemotherapy; non-Hodgkin's lymphoma; surgery

INTRODUCTION

The earliest report of gastrointestinal (GI) lymphoma is by Dr. Thomas Bilroth in 1871 [1]. The gastrointestinal tract is the largest immunologic organ and is the most common site of extranodal involvement by non-Hodgkin's lymphoma, accounting for 50% of all extranodal cases. Primary GI lymphoma represents ~5% of all primary GI tract tumors [2–4], 20% of small bowel tumors, 2.5% of gastric and 0.4% of colonic cancers [5]. The annual incidence of primary GI lymphoma ranges from 1 to 1.5 persons per 100,000 adults [6–8].

The optimal treatment of primary GI lymphoma is yet to be determined. There have been very few randomized prospective clinical trials. The objectives of this study are to assess the survival differences among GI lymphoma patients treated with different modalities and to determine how stage, grade, and location of disease in the GI tract affect prognosis.

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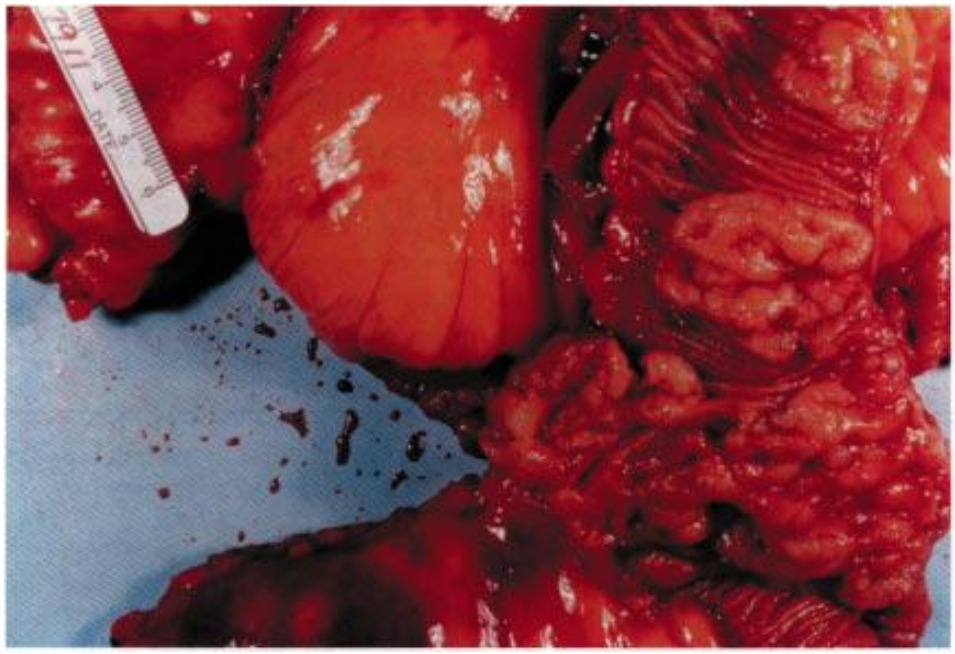

Fig. 1. Gross specimen of small bowel lymphoma.

TABLE I. Histologic Grade of Gastrointestinal Lymphoma (working formulation)* [10]

High	Intermediate	Low
Diff immuno lg cell	Diffuse/foll lg cell	Foll cleaved sm cell
N = 23	N = 36	N = 6
Diff noncleaved sm cell	Diff lg, sm cells	Foll lg, sm cell
N = 9	N = 4	N = 0
Histiocytic/lymphoblastic cell	Diff cleaved sm cell	Lymphocytic sm cell
N = 0	N = 1	N = 9

*See Ref. 10. Undetermined grade N = 12. Diff = diffuse, lg = large, foll = follicular, sm = small.

MATERIALS AND METHODS

Primary GI lymphoma was mainly diagnosed and staged during exploratory laparotomy with surgical resection, but also by endoscopic biopsy plus computed tomography. Staging was based on the Ann Arbor classification [1], specific for GI lymphomas: Stage IE—single GI tumor focus without nodal involvement, Stage IIE—GI tumor focus with nodal involvement on one side of the diaphragm, Stage IIIE—GI tumor focus with lymph node involvement of both sides of the diaphragm, and Stage IVE—GI tumor focus with diffuse or disseminated involvement of one or more extralymphatic organs (i.e., bone marrow, lungs, liver).

Histologic grade was defined by the Working Formulation [9] (Table I). The location of GI lymphoma was grouped by stomach, small bowel, and colon. A total of 100 patients, ages 13–93 years (mean age 62.4 years) and male to female ratio of 1.08, were diagnosed with primary GI lymphoma and treated from 1980 to 1993 at Providence Hospital (Southfield, MI) and Hartford and St. Francis Hospitals (Hartford, CT), with a median follow-up of 5 years (range 2–8 years).

There were 21 Stage I patients, 28 Stage II, 11 Stage III, 36 Stage IV, and 4 with undetermined stage. Thirty-two patients presented with high histologic grade, 41 with intermediate grade, 15 with low grade, and 12 with undetermined grade. The vast majority of the histologic type were B-cell lymphoma of mucosa-associated lymphoid tissue. GI lymphoma was located in the stomach in 57 patients, small bowel (Fig. 1) in 32 patients, and colon in 12 patients. The mode of therapy for the various stages and locations of disease are listed in Tables II and III.

Surgery consisted of wide local resection of the primary tumor (curative for Stages 1 and 2, and palliative for Stages 3 and 4), and regional lymph nodes, with re-establishment of bowel continuity. Chemotherapy involved 8–10 courses of cyclophosphamide, adriamycin (hydroxydaunorubicin), vincristine (oncovin), and prednisone (CHOP). The treatment selection of patients was based primarily on the stage of GI lymphoma at presentation, followed by the patient's overall health status and physician's preference. For Stage I, 76% of patients underwent curative resection alone. For Stage II, 46% received curative resection plus adjuvant chemotherapy. For Stage III, 27% of patients underwent palliative resection plus adjuvant chemotherapy. Last, for Stage IV, 36% of patients received palliative resection plus adju-

TABLE II. Mode of Therapy for Gastrointestinal Lymphoma and Stage of Disease

Stage	Surgery	Surgery/ chemotherapy	Chemotherapy	No. treatment
I	16	3	2	0
II	13	12	3	0
III	4	3	4	0
IV	6	13	13	4
Unknown	3	0	1	0
	N = 42	N = 31	N = 23	N = 4

TABLE III. Mode of Therapy for Gastrointestinal Lymphoma and Location of Disease

Location	Surgery	Surgery/ chemotherapy	Chemotherapy	No. treatment
Stomach N = 57	25	13	15	4
Sm bowel N = 31	14	12	5	0
Colon N = 12	6	4	2	0

vant chemotherapy, and 36% received primary chemotherapy.

The Chi-square method was used for statistical analysis of the data.

RESULTS

The 5-year actuarial survival of GI lymphoma patients treated with surgery alone, surgery plus adjuvant chemotherapy, primary chemotherapy, and those without treatments were 57%, 76%, 58%, and 0%, respectively (Fig. 2). When considering different stage, grade, and location of disease, there were no statistical differences in 5-year actuarial survival. In our series, surgery with adjuvant chemotherapy was found to be the superior treatment over surgery alone or primary chemotherapy with better 5-year survival (Fig. 2, $P < 0.05$). Moreover, primary chemotherapy was shown to be as effective as primary surgical resection with similar 5-year survival.

Diffuse or follicular large cell (N = 36, intermediate grade) was the most common histology, followed by diffuse immunoblastic large cell (N = 23, high grade) (Table I). Abdominal pain, GI bleed, and weight loss were the most common presenting symptoms.

There were three surgical mortalities (4.1%) and 14 morbidities (19.2%) (Table IV). The morbidities for chemotherapy (adjuvant and primary) were 15 (27.7%) (Table V).

DISCUSSION

Historically, surgery has been the mainstay of treatment for GI lymphoma [10–14]. Curative resection for gastric and intestinal lymphoma has been shown to be

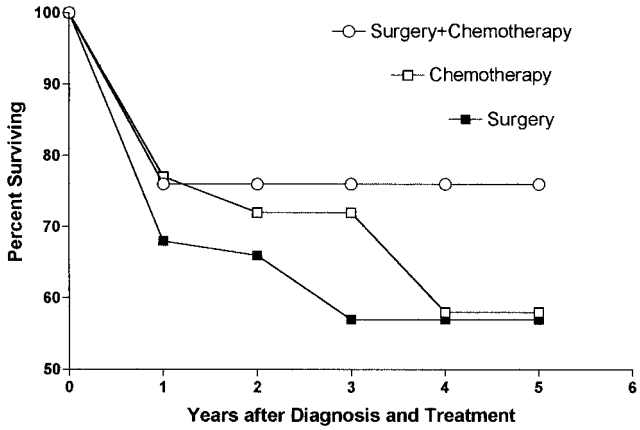

Fig. 2. Actuarial survival of patients receiving surgery, chemotherapy, or surgery plus chemotherapy for treatment of gastrointestinal lymphoma.

TABLE IV. Primary Gastrointestinal Lymphoma: Surgical Complications (N = 73 patients)

Mortality	3	(4.1%)
Morbidity:		
small bowel obstruction	4	(5.4%)
wound infection	5	(6.6%)
anastatomic leak	3	(4.1%)
anastatomic bleed	2	(2.7%)
total morbidities	14	(19.2%)

TABLE V. Primary Gastrointestinal Lymphoma: Chemotherapy Complications (N = 54 patients)

Morbidity:		
chronic diarrhea	4	(7.4%)
upper gastrointestinal ulcer	2	(3.7%)
small bowel stricture	2	(3.7%)
catheter site sepsis	1	(1.8%)
neutropenic sepsis	1	(1.8%)
perforation	2	(3.7%)
gastrointestinal bleed	3	(5.5%)
total morbidities	15	(27.7%)

superior to palliative resection in terms of survival [15,16] (Table VI).

Surgery plus postoperative radiation, either whole abdominal or locoregional did not show a survival advantage over surgery alone for gastric lymphoma [15,17,18]. The role of surgery has been challenged for treatment of early stage gastric lymphoma. Primary radiation therapy has been shown to have similar survival to surgery plus postoperative radiation for stage 1 and 2 gastric lymphomas [19]. Maor and associates in 1990 demonstrated a 62%, 5-year disease free survival for 34 stage 1 and 2 gastric lymphoma patients who underwent ''sandwich'' multimodality therapy. This involved four cycles of CHOP-bleo, followed by 4,000 cGy, and was concluded by eight cycles of CHOP-bleo [20].

The role of surgery with adjuvant chemotherapy ap-

TABLE VI. Actuarial Survival Based on Various Modalities of Treatment for Gastrointestinal Lymphoma in the Literature

Study	Number	Treatment[a]	5-year survival[b]
Surgery			
[27]	84 Gastric	Curative	75%
		Palliative	32%
[16]	97 Intestinal	Curative	48%
		Palliative	12%
Surgery/radiation			
[19]	119 Stage 1 & 2 gastric	Surgery/rad	82%
		Radiation	71%
[15]	58 Gastric	Surgery	65%
		Surgery/rad	67%
[28]	Colo/rectal	Surgery/rad	35%
Surgery/chemo			
[22]	26 Stages 1 & 2, gastrointestinal	Surgery/Chemo	84%
[23]	10 Stage 1; 4 Stage 2; 4 Stage 4, gastric	Surgery/Chemo	94% (DF)
Chemotherapy			
[26]	18 Stage 4, gastric	CHOP-bleo or CHOP	78% (4 yr)
[25]	56 Stage 1 & 2; 35 Stage 4, gastrointestinal	ACVB	62% (4 yr)
Chemo/radiation			
[20]	34 Stage 1 & 2, gastric	CHOP-bleo 4× + radiation (4000 cGy) + CHOP-bleo 8×	73% & 62 % (DF)

[a]CHOP-bleo = Cyclophosphamide, adriamycin, vincristine, prednisone, bleomycin; ACVB = Adriamycin, cyclophosphamide, vincristine, bleomycin.
[b]DF = disease-free.

pears promising with higher survival figures than other treatment modalities in the literature. A survival advantage of surgery with adjuvant chemotherapy has been seen in patients with high risk Stage 1 (high grade histology, tumor invasion of serosa, >5 cm tumor size) or Stage 2 GI lymphoma [21–23].

To date, the best results in the literature have been reported by Sheridan et al., with a 94%, 5-year disease-free actuarial survival in 18 Stage 1 to 4 gastric lymphoma patients treated with surgery plus adjuvant chemotherapy (CVP for early stage and CHOP for advanced stage) [23]. In our series of 100 GI lymphoma patients of all stages and grades, surgery (curative or palliative) plus chemotherapy (CHOP, 8–10 cycles) ($P < 0.05$, Table I) showed a 5-year survival advantage over either surgery or chemotherapy alone.

Currently, primary chemotherapy is considered by some to be the procedure of choice in Stages 3 and 4 of GI lymphoma, although surgical debulking may lessen the risk of complications from chemotherapy, such as bleeding or perforation [24,25]. Solidoro and associates reported a 78%, 4-year survival for 18 Stage 4 gastric lymphoma patients treated with CHOP or CHOP-bleo [26].

Our data confirm the effectiveness of primary chemotherapy, showing near identical survival at 5 years when compared to surgery alone for treatment of gastrointestinal lymphoma of all stages and grades (n = 100, Table I).

A significant number of patients in our study presented with stage IV GI lymphoma (n = 36). Thus chemotherapy serves as an important part of the treatment plan either as a primary modality or as adjunctive therapy after surgical debulking (palliative resection).

Of note, all four stage IV gastric lymphoma patients in our series who received no treatment, failed to survive more than 6 months from the time of diagnosis.

Conclusions

We conclude that surgery, when feasible, with adjuvant chemotherapy for GI lymphoma offers the best survival result over other modalities. However, in poor-risk patients, primary chemotherapy offers an effective alternative.

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